Please add the following claims:

~~11.~~ The method according to Claim 7 wherein the composition is in the form of an aqueous suspension for oral administration.

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12. The method according to Claim 11 wherein the monohydrate has a purity of at least 90%.

13. The method according to claim 12 wherein the monohydrate is administered in an amount of 125mg to 1 gm, one to three times daily.

14. A method of prophylactic treatment of a herpes viral infection in a mammal in need thereof, which method comprises the administration to said mammal of an effective amount of a pharmaceutical composition comprising famciclovir monohydrate, and a pharmaceutically acceptable carrier.

15. The method according to Claim 14 wherein the composition is in the form of an aqueous suspension for oral administration.

16. The method according to Claim 15 wherein the monohydrate has a purity of at least 90%.

17. The method according to claim 16 wherein the monohydrate is administered in an amount of 125mg to 1 gm, one to three times daily.

REMARKS

In response to the Examiner's Office action of 13 June 2000, which was made final, Applicants respectfully submit herewith a continuation application in which the claims have been amended to claim the method of use of famciclovir monohydrate for the treatment of herpes viral infections. Claims 1 to 6 and 8 to 10 have been cancelled. Claim 7 has been amended to correspond to claim 17 in the parent application, and newly added claims 11 to 17 are of similar dependencies.

Support for claim 11 lies in the specification on page 2, lines 26 to 28. Support for claim 12 lies on page 1, line 29 of the specification. Support for claim 13

lies in page 2, line 31 of the specification. No new matter is believed added. Applicants reserve the right to file divisional or continuation application on cancelled or deleted subject matter.

Applicants wish to respond to the prior office action in parent application 09/117,823 in this preliminary amendment as the claims have been amended to further prosecution on the merits and advance the case to issuance.

Rejection under 35 USC §102/103

In the parent application Claims 5, and 12 to 17 stood rejected under 35 USC §102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as being obvious over Harden *et al.* reference.

In Applicants previous response of October 12, 1999 in parent 09/117,823 clarification of which Harden *et al.* reference was requested. No specific response to this request is stated by the Examiner, however the rejection did indicate page 1739 which would imply that the rejection is based on *J. Med. Chem.*, 1989, 32(8), 1738 –43 article. Therefore, Applicants respectfully traverse this rejection over the J. Med. Chem. reference. Claims 5, 12, and 14 to 26 were directed to a pharmaceutical composition comprising FCV monohydrate, in a pharmaceutically acceptable carrier in the form of an aqueous suspension for oral administration. Claims 13 and 17 however, were directed to the use of the pharmaceutical composition of Claim 5 for treatment of a viral or herpes viral infection and hence this rejection is still relevant to the claims herein.

Compound 14 of the Harden *et al.*, J. Med. Chem. reference is famciclovir anhydrate and is not the monohydrate form, as confirmed by the elemental analysis shown therein. This is also evident from the discussion in the last paragraph of page 1739.

The Harnden *et al.* reference clearly states that compound 14 is being evaluated in clinical trials (page 1736, last sentence of the abstract). Page 1741-1742 of the experimental section describes the synthesis and analysis of compound 14. Elemental analysis clearly shows that compound 14 is the anhydrous form of famciclovir, and not the monohydrate. The chemical formula of compound 14 derived from the elemental analysis is given as $C_{14}H_{19}N_5O_4$ (i.e. famciclovir), famciclovir monohydrate has the formula $C_{14}H_{21}N_5O_5$.

In furtherance of this analysis, Applicants enclose herewith a signed declaration of Michael John Raw that addresses the issue of elemental analysis and the differences between FCV anhydrate and FCV monohydrate. This declaration shows that the expected elemental analysis of FCV anhydrate is $C_{14}H_{19}N_5O_4$ as discussed above, and the expected elemental analysis of FCV monohydrate is $C_{14}H_{21}N_5O_5$. The Harnden et al. reference teaches a

synthetic route which produces a compound 14 that yields the anhydrate and not the monohydrate form of famciclovir.

The Harnden *et al.* reference on page 1741 discuses certain compounds selected as potential oral prodrugs for antiviral activity, and specifically indicates in the first full paragraph of the right-hand column that compound 14 was identified as "the preferred prodrug for oral administration, and this compound is now being evaluated in clinical trials". That identification was of famciclovir anhydrate, compound 14 as described in the synthetic examples.

It should be noted that the commercial form of famciclovir being marketed is the anhydrous form, and the commercial form had been the one used in the clinical trials (on which the paper is based), and for which the approval was obtained.

Therefore, the Harnden *et al.* reference does not anticipate the claims of the present application.

In order for the Harnden *et al* publication to be anticipatory, the document must disclose all the aspects of the claim. This document does not disclose the use of a pharmaceutical composition of famciclovir monohydrate, as required by the claims herein, and therefore is not anticipatory. Reconsideration and withdrawal of the rejection to the claims currently in this application is respectfully requested.

As to the rejection of the Claims 5, and 12 to 17 as being obvious under 35 USC §103 over the Harden *et al.* reference, Applicants also respectfully traverse this rejection for similar reasons as above.

The present invention is directed to use of a pharmaceutical composition of famciclovir monohydrate, for the treatment of viral infections. Applicants have demonstrated in the present invention that famciclovir monohydrate possesses unexpected properties, as illustrated in the test results given on page 4 of the specification. While the Examiner comments that the data presented on page 4 is not sworn to, this is not correct. The application contains a declaration by the inventors.

Page 4 of the description demonstrates famciclovir monohydrate as compared to famciclovir anhydrate in a suspension formulation. Famciclovir anhydrate, although stable when formulated as tablets or capsules, exhibits unacceptable crystal growth when used in suspension formulations. The test results show that crystals of famciclovir anhydrate increased in size by ten fold in a week. Crystal growth is unacceptable in a suspension since it alters the particle size distribution of the suspension.

Surprisingly it has been found that famciclovir monohydrate exhibits little or no crystal growth when formulated in a suspension. This is neither taught nor suggested by Harnden *et al.*

Famciclovir anhydrate has an initial aqueous solubility in excess of 25% w/v but will then precipitate out as the monohydrate form that has a solubility of approx. 2.2%. Table 1, below, shows the effect of pH on the solubility of famciclovir monohydrate.

Table 1: Solubility v. pH for Famciclovir Monohydrate

pH	2	4	6	7	8	10	12
Solubility (%w/v)	32.2	2.5	2.2	2.2	2.3	2.6	2.7

The table clearly shows that the solubility at 25°C between pH 4 and pH 12 is consistently between 2.2 and 2.7% w/v.

The two compositions in the table on page 4 of the present application were formulated to give approximately a 5%w/v famciclovir suspension and a pH of approximately 6 to 7. In the case of the monohydrate formulation, initially some of the monohydrate will go into solution (up to 2.2%) with the remainder staying in suspension. Here, the particle size in the suspension is controlled by that of the starting material. However for the anhydrous famciclovir formulation all of the famciclovir will go into solution and then over time will precipitate out the monohydrate form thus giving the potential for crystal growth (with potential uncontrolled particle size) as observed in this study.

The Examiner maintains that the data on page 4 of the description is of no real value because of differences in how the two compositions were formulated, and the assumption that the two compositions did not have the same acidity. Applicants maintain that the concentration of famciclovir in the product is virtually the same with the monohydrate suspension containing 33.4%w/v famciclovir and the anhydrate formulation containing 33.3%w/v.

With regard to the acidity of the two compositions, it should be noted that the anhydrate form of disodium hydrogen phosphate (not the dihydrate) was used for the famciclovir anhydrate formulation. In both cases, however, the concentration would be equivalent to

approximately 15.6% disodium hydrogen phosphate (anhydrous). Therefore the pH of the systems would be very similar.

The difference in the levels of silicon dioxide in the two formulations is because it is the "make weight" being added as necessary to give similar weights of powder per composition. Silicon dioxide is essentially insoluble and considered to be inert in the formulation.

The Applicants maintain that the data on page 4 of the present application is a valid comparison demonstrating the differences in crystal growth properties of famciclovir monohydrate and famciclovir in suspension formulations.

The Examiner has also rejected the product by process claim, claim 14. As Applicants have cancelled claim 14 this renders the rejection moot. Applicants will continue prosecution of the pharmaceutical composition and process claims in a divisional application.

In view of these Remarks and submission of the Raw Declaration, reconsideration and withdrawal of the rejection to the claims under 35 USC §103 is respectfully requested.

Rejection under 35 USC §112

Claims 13 and 17 were rejected under 35 USC §112, first paragraph, as being non-enabling for other viruses besides HSV-1, HSV-2 and VZV. Applicants respectfully traverse this rejection.

The Examiner maintains that "penciclovir is simply not effective against any important herpes viruses such as EBV, HVS, HHV-8 and CMV". This is an incorrect statement as the following publications demonstrate the efficacy of penciclovir against EBV, HHV-8 and CMV. The Applicants are unclear as to which particular virus the Examiner is referring to when he refers to "HVS", presumably this is HSV? Copies of these references accompany the filing of this application and response.

Bacon et al (T.H. Bacon and M.R. Boyd, *Antimicrobial Agents and Chemotherapy,* 1995, **39(7)**, 1599-1602) shows that penciclovir is active against Epstein-Barr virus (EBV). The EC_{50} (50% effective concentration) is given as 2.3μg/ml (see abstract).

Boyd et al (M.R. Boyd, T.H. Bacon, D. Sutton and M. Cole, *Antimicrobial Agents and Chemotherapy,* 1987, **31(8)**, 1238-1242) discloses an EC_{50} value for penciclovir [also known as BRL 39123 and 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine] against cytomegalovirus

(CMV) of 52μg/ml, showing that penciclovir is active against CMV (see abstract and table 1, page 4239).

Neyts et al (J. Neyts and E. De Clercq, *Antimicrobial Agents and Chemotherapy,* 1997, **41(12),** 2754-2756) demonstrates that penciclovir has inhibitory effects against human herpesvirus-8 (HHV-8) with an EC_{50} of 40μM (corresponding to approximately 11μg/ml) (see abstract and table 1, page 2755).

The Examiner's reasoning that the specification does not enable any person skilled in the art to use the invention commensurate in scope with the claims appears to be that (1) it has not been shown that any antiviral agent can be used to treat herpesvirus infections generally, and (2) it is therefore impossible to show that FCV monohydrate can be used to treat herpesvirus infections generally. Both the premise and the conclusion of this analysis are flawed.

The present invention is directed to a particular form of famciclovir, the crystalline monohydrate form, filed in provisional application in 1996. At the time of this invention, it was well recognized by the skilled artisan that penciclovir and famciclovir were useful in the treatment, generally of known herpetic agents, such as HSV-1, HSV-2, CMV, EBV, and VZV. It was also well known that PCV, and FCV belong to a class of compounds, the acyclic nucleosides, which also include such compounds as acyclovir (ACV), and ganciclovir (GCV). ACV, GCV and PCV have been shown to inhibit the DNA polymerases of herpesviruses, thereby decreasing viral replication and production of infectious herpesviruses in infected cells and spread of the virus. The acyclic nucleosides can therefore be used to treat herpesvirus infections. At the time of filing of Applicant's patent application for the compound penciclovir (PCV) in 1984, both ACV, GCV and had been shown to be broad spectrum antiherpes agents having activity against each of the human herpesviruses known at the time that application was filed.

The papers shown herein, and other well known data in the art, clearly demonstrate that FCV, and by metabolism PCV, is in fact a general antiherpes agent, i.e., that it can be used to treat herpesvirus infections. For example, PCV has previously been shown to be moderately to highly active against all five of the human herpesviruses (HSV-1, HSV-2, VZV, CMV, and EBV) known at that time. PCV has also been shown to be highly active in inhibiting a number of animal herpesviruses against which it was tested. In addition, PCV has been shown to have activity against human herpesvirus 6 (HHV-6) and human herpesvirus 8 (HHV-8). While PCV may be more active against certain herpesviruses, e.g., HSV and VZV, than others, the majority of herpesviruses are inhibited by PCV, and PCV is therefore a general antiherpetic agent.

Therefore, in light of these remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, first paragraph is respectfully requested.

Rejection under 35 USC § 112, second paragraph

Claim 16 was rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out the subject matter of the invention. Applicants respectfully traverse this rejection.

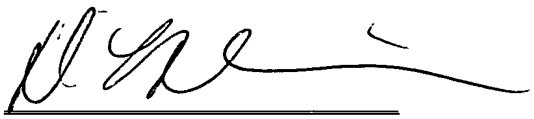
While it is believed that routine experimentation can readily determine the concentration of water vapour necessary for crystallization, the claim has also been cancelled in order to advance prosecution on the merits. However, it should be noted that the term "high" will be deleted in this claim and amended (in a divisional application) to read on a "sufficient concentration" of water vapour. As noted, it is believed that routine experimentation is all that is necessary to find out what concentration would be sufficient to work.

As the claim has been cancelled, this rejection is rendered moot. A divisional application will be filed to continue prosecution on this issue.

Conclusion

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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